

Exhibit 1
Declaration of Stanley J. Watson, M.D., Ph.D.

I, STANLEY J. WATSON, M.D., Ph.D., do hereby declare as follows:

1. I am Professor & Research Scientist, Department of Psychiatry and Mental Health Research Institute, University of Michigan (1987 – Present); Associate Chair for Research, Department of Psychiatry, University of Michigan (1993 – Present); and Co-Director, Mental Health Research Institute, University of Michigan (1995 – Present). I received my Ph.D. in Clinical Psychology from the University of Iowa in 1970 and my M.D. from Tulane Medical School in 1974. I am licensed to practice medicine in the states of Louisiana, California and Michigan. I am Board Certified in Psychiatry and Neurology. I have been and am on the Editorial Boards of several journals, including: Neuropsychopharmacology; Critical Reviews in Neurobiology; Molecular Neurobiology; and Peptide Research. Since 1997, I have served as Chair, Board of Scientific Counselors for the National Institute of Mental Health. I am a Member of the Institute of Medicine of the National Academy of Sciences; Society for Neuroscience; and the International Society for Neurochemistry. I have been an invited presenter at over 100 scientific conferences. I am an author and/or co-author of over 300 scientific papers. A copy of my Curriculum Vitae is attached to my declaration as **Appendix A**.
2. Through my research activities, I am very familiar with G protein-coupled receptors (“GPCRs”) and the role of GPCRs in modulating biological effects in living organisms, including humans, as well as the importance of GPCRs as a class of receptors useful for drug discovery purposes.
3. Two of the co-founders of Arena Pharmaceuticals, Inc., Michael E. Lewis, Ph.D. and Derek T. Chalmers, Ph.D., conducted post-doctoral training in my laboratory at the University of Michigan. I have maintained, and continue to maintain, a personal and professional relationship with Drs. Lewis and Chalmers. Via stock options provided to me, I own Arena common stock; these stock options were not provided to me in connection with this declaration, but rather in connection with consulting activities that I provide to Arena.
4. I am familiar with Arena’s technology for direct identification of inverse agonists and agonists using both orphan and known GPCRs. I am familiar with Arena’s patent application entitled “A Method of Identifying Modulators of Cell Surface Membrane Receptors Useful in the Treatment of Disease.” At the request of Arena, I have reviewed a document prepared by the US Patent & Trademark Office (“PTO”), referred to as an “Office Action”, and in particular, the position taken by the PTO in Paragraph 4 of the Office Action.
5. I have been asked by Arena to provide an opinion as to the scientific positions taken by the PTO in the Office Action. In this context, my declaration relies upon the use of certain terms and phrases that are used by the PTO in the Office Action. My use of these terms and phrases is intended to provide a “common language” link between my declaration and the Office Action. For example, while I refer to the phrases “well established utility” and “real world use” in my declaration, this is because these phrases are used by the PTO following the scientific analysis presented by the PTO in the Office Action. Accordingly, while my declaration is based upon a scientific analysis, for convenience and where appropriate, I use the same terms and phrases used by the PTO in the Office Action.

6. Based upon my educational and scientific background, it is my opinion that the positions taken by the PTO to support its view that there is not a well established utility for the claimed invention can not be supported from a scientific perspective. Therefore, I do not agree with the conclusions reached by the PTO that there is not a well established utility for Arena's claimed invention.

7. Based upon my review of the Office Action, the PTO has taken the following position with respect to Arena's claimed invention: "there is not a well established utility for the claimed invention." This position is apparently based upon the conclusion of the PTO that the claimed invention does not provide a utility that provides a "real world use." This conclusion is supported by the PTO in the Office Action as follows:

- a. Because an orphan receptor does not have by definition a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease states.
- b. Similarly, constitutively activated orphan receptors have no known function.

Based upon these two positions, the PTO asserts the following:


Thus, the asserted utilities are essentially methods of identify[ing] lead compounds which affect constitutively activated orphan receptor activity, which does not define a "real world" context of use. Therefore, identifying compounds that interact with orphan receptors would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use.

The PTO then concludes with the following statement:

Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the method of identifying compounds having activity of inverse agonist or agonist activity, further experimentation is necessary to attribute a utility to constitutively activated orphan receptors and to the compounds that bind the constitutively activated orphan receptors.

8. In my opinion, several scientific misconceptions have been presented by the PTO in support of its position. Consequently, it is my opinion that the conclusions reached by the PTO are incorrect and can not be supported.

9. While I certainly appreciate that the PTO is not expected to have a working knowledge of many of the scientific areas in which it is required to provide an analysis, nevertheless it is important in the context of certain positions taken by the PTO to provide




some constructive correction. The drug discovery process is not, as implied by the PTO, a perfect process. Very few pharmaceuticals are approved based upon a clear and precise understanding of how the drug “works” in the body. Indeed, our complete understanding, if any, of how drugs “work” is often based upon empirical evidence after the drug has been approved and is on the market. In this context, it is simply not plausible to assume that the drug discovery process is defined by a mechanistic approach, i.e., by finding a receptor and an endogenous ligand for that receptor one can then define the mechanism of the receptor-ligand interaction and therefore use this mechanism to precisely define how a potential drug will work. The major requirements used by the FDA for drug development are safety and efficacy where, in the vast majority of cases, the mode of action of drugs are simply not known.

10. Receptor-endogenous ligand-based drug discovery often involves a mass screening approach and serendipity, which is simply an approach based upon tradition of reasonable success – and certainly not any exclusive rules. As our understanding of the human genome evolves, so too does our understanding of receptor-based communication, and therefore, our ability to utilize new approaches, i.e., non-traditional approaches to drug discovery will become increasingly valuable. In my opinion, Arena’s claimed invention is based upon a non-traditional approach that takes advantage of an understanding of receptor-based communication and not a traditional, receptor-endogenous ligand interaction approach.

11. The advantages of Arena’s invention are, in my opinion, particularly evident in the area of orphan receptors, i.e., receptors for which the endogenous ligand has not as of yet been identified. To imply, as the PTO has done, that one absolutely must have access to the receptor’s endogenous ligand to understand the function of the receptor is simply incorrect. Where a receptor is expressed; the systems and circuits within which a receptor is located; how the receptor is expressed in a normal versus a disease state; and changes in receptor expression in response to certain conditions -- all of these provide a plethora of information that, in my opinion, can readily guide a scientist having routine skill to an understanding of the function of the receptor, without an absolute requirement of knowing the endogenous ligand for the receptor. Certainly having access to a receptor’s endogenous ligand is useful in securing and understanding of receptor function, but such access is not required in order to understand receptor function. To put a fine point on it, because orphan receptors exist in biological tissues having ascertainable functions; because orphan receptors have specific and ascertainable effects on cellular signaling; and because orphan receptors are altered in number and perhaps form by the genome in response to physiological stimuli, the function of an orphan receptor can be ascertained upon selection of an orphan receptor of interest. All of these powerful classes of useful information can be derived based upon a particular orphan receptor of interest, and can be readily determined using routine techniques, such as those described in the patent application as well as others that are well known in the art.

12. Because of these and other factors, it is my opinion that those in the drug discovery business are now recognizing the value of initiating the drug discovery process using orphan receptors, rather than waiting years until the endogenous ligand for the receptor is identified. Indeed, this is an important, and increasingly recognized use, for the invention claimed in the present patent application.



13. As a way of explaining this opinion without focusing on the claimed invention itself, I note that in early 2000, scientists employed by one of the world's leading pharmaceutical companies, Glaxo Wellcome, Inc., published a paper entitled, "Use of Constitutive G Protein-Coupled Receptor Activity for Drug Discovery." Chen, G. et al. *Mol. Pharm.* 57:125-134 (2000). In the paper, the following was noted:

"The data presented with these [known] receptors indicate that a constitutive GPCR assay is a viable alternative for screening orphan receptors. The advantage of such an approach lies in the expanded window of detection. Not only will agonists be found but also inverse agonists. This option is not available in nonconstitutively active screens in which only positive agonists will be detected.

"These data are consistent with the idea that constitutive GPCR systems can be made sufficiently sensitive and stable to be used for screening for ligands. The fact that all but one of the [known] receptors we tested provided substantial constitutive activity suggests that this approach would be especially useful for the screening of orphan receptors." *Mol. Pharm.* at 131-132.

14. In my opinion, the limitations of traditional receptor-based drug discovery techniques that mandated access to a receptor's endogenous ligand have been, and are increasingly being, recognized as limitations, not requirements. Access to the receptor's endogenous ligand is not per se required to understand the putative function of the receptor; indeed, in my opinion, because of the increasing awareness of the circuit-based relationship between receptors, it is the location (e.g., cell or tissue type) of the receptor that is more telling to this issue, and not just its endogenous ligand. And in addition to companies such as Eli Lilly and Company who have licensed Arena's claimed technology, since companies such as Glaxo Wellcome have publicly asserted the utility of using constitutively active orphan receptors for the discovery of inverse agonists and agonists, it seems to me that to the position taken by the PTO that the invention claimed by Arena has no "real world use" is by definition unsupportable.

15. Prior to addressing the specific positions taken by the PTO, I note that the claims are focused on identification of "inverse agonists" and "agonists" and not "antagonists." This is, in my opinion, important. GPCRs are signal-transducers, that is, these receptors exist to allow for cell-to-cell communication, and in some cases used to feedback to the releasing cell the amount of endogenous ligand released by that cell. Until relatively recently, the scientific community generally assumed that GPCRs possessed no signal-transducing capacity until activated by an agonist i.e., GPCRs were "off" in terms of signal-transduction until turned "on" by an agonist, generally the receptor's endogenous ligand. Yet we now know that signaling systems within cells have a rich range of basal and endogenous ligand-induced post-signaling control steps (GTPase activity of RGSSs, arrestins and different specific G protein modulatory chemistry) which can modulate cellular signaling states. Based upon the previous simplistic, and incorrect view, a presumption has existed that in order to keep GPCRs in an "off" state, one should search for an antagonist, e.g., a compound that prevented the GPCR's endogenous ligand from binding to the GPCR. Thus, this mode of thinking, by definition, has forced the scientific community to assume, incorrectly, that one can not identify GPCR modulators without first having access to the GPCR's endogenous ligand.

16. Those in the art appreciate that "inverse agonist activity" can drive a GPCR's intracellular signaling below its normal baseline. An important example of this is the existence of naturally occurring inverse agonist activity at two known GPCRs in the same family. To be clear, in the brain there is a balance between the POMC-MSH neuropeptide system and the AGRP neuropeptide system. Both of these systems act on MC3 and MC4 melanocortin GPCRs to alter feeding behavior in mammals. The POMC system is a powerful inhibitor of feeding. For example, there are published data evidencing that defects in either the processing enzymes in POMC or the receptor for POMC products leads to increased feeding, and, as has been reported, children who are less than five years of age who have defects in this system consume food in an abnormal manner and weigh several hundred pounds. The AGRP system actively reverses the effects of POMC produced peptides which act on cells that contain MC3 and MC4 receptors; thus, this inverse agonist activity of AGRP prevents POMC effect, thereby allowing very active eating on the part of the mammal. Hence, the signaling set point of the neuron with POMC receptors can be completely on, completely off or even set between on and off based upon natural agonist and natural inverse agonist activity.

17. With the foregoing in mind, I note that it has only been within about the past decade that the scientific community has begun to more fully appreciate that the conformational states of GPCRs exist in equilibrium between a basal state (generally referred to as "R") where receptor function is inactive, and an active state (generally referred to as "R*") where the receptor is able to function (i.e., transduce a signal), and that the "shape" of the receptor shifts between these two conformations. This understanding thus explains why GPCRs are capable of function even in the absence of endogenous ligand binding to the receptor, i.e., constitutively active GPCRs. In this context, the scientific community has begun to understand that the presence and the maintenance of the active state R* is promoted by binding of an agonist, such as the endogenous ligand, while the presence and maintenance of the inactive state R is promoted by binding of an inverse agonist. Thus, an agonist shifts the equilibrium of the GPCR to R*, while an inverse agonist shifts this equilibrium to R. A true antagonist is a compound that binds to the receptor but does not shift the equilibrium, i.e., a true antagonist merely prevents the endogenous ligand from binding to the receptor, but even though it binds to the receptor, a true antagonist has no intrinsic effect on receptor equilibrium per se. Because virtually all known endogenous ligands for GPCRs are agonists, the equilibrium of most GPCRs is generally understood to favor the inactive state R, such that cells expressing a GPCR of interest can respond to the presence of the endogenous ligand by increasing the proportion of active state R* and thus increase the functional response of the cell upon endogenous ligand binding. Because most GPCRs favor the inactive state, antagonists do not directly impact the function of the cell, but rather prevent the equilibrium shift to R* by preventing the endogenous ligand from binding to the receptor. Indeed, in terms of obtaining compounds that are intended to directly impact the function of the cell, the equilibrium states of GPCRs naturally mandate that one should obtain inverse agonists (to maintain the receptor in an inactive R state) or agonists (to maintain the receptor in an active R* state) – **this approach favors avoidance of the use of the receptor's endogenous ligand**. Indeed, it is now appreciated that true antagonists are rare, and that the majority of antagonists are presumed or have been demonstrated to be compounds that possess some

degree of inverse agonist activity. In other words, by “accident”, the use of endogenous ligand-based receptor screening has indirectly led to the discovery of compounds that possess the preferred inverse agonist characteristics. Thus, classical competitive binding assays that use the receptor’s endogenous ligand can actually **impede** the discovery of a more effective and beneficial inverse agonist compound, because binding assays are intrinsically unable to measure inverse agonist and agonist activity.

18. Thus, when the PTO takes the position that “further experimentation is necessary to attribute a utility to...the compounds that bind the constitutively activated orphan receptors” it is my opinion that this position is incorrect with respect to an inverse agonist or an agonist. In my opinion, by focusing on mere “binding” the PTO has inappropriately skewed its analysis to binding affinity, i.e., the ability of a compound to interact with a receptor, rather than functionality, i.e., the ability of a compound to alter the function of a receptor. An “inverse agonist” is understood to define a compound that impacts the function of a receptor, i.e., an inverse agonist will shift the equilibrium of the GPCR to an inactive state. An “agonist” is understood to define a compound that also impacts the function of a receptor by shifting the equilibrium of the GPCR to an active state. “Binding” merely indicates that a compound interacts with a receptor, but provides absolutely no indication of what, if any, impact the compound would have on the function of a receptor. In other words, in my opinion, the claims of the Arena patent application, because they are directed to “inverse agonists” and “agonists” and not antagonists, define a utility for the compound classes – i.e., an inverse agonist of a constitutively activated orphan receptor, by definition, shifts the equilibrium of the receptor to an inactive state to reduce the functional activity of the receptor, while an agonist of a constitutively activated orphan receptor, by definition, shifts the equilibrium of the receptor to an active state to enhance the functional activity of the receptor. An antagonist is classically defined by its ability to block an agonist from binding to the receptor. To put a fine point on it, inverse agonists and agonists for constitutively activate receptors can in fact be directly identified because they impact the receptor’s normal downstream signaling systems. Because these downstream signaling systems are based upon proteins, i.e., G proteins, and because different G proteins provide different types of measurable signals, it is simply not correct to imply that one can not understand what proteins are modulated by an orphan GPCR - indeed, in my opinion a part of the importance of the claimed invention, in addition to serving as lead drug candidates for drug discovery purposes, is that inverse agonists and agonists discovered using the claimed method provide a crucial and important understanding of the connection to cellular signaling response elements.

19. As the scientific community has begun to appreciate these concepts, the concept of constitutively active GPCRs has begun to make scientific sense, i.e., GPCRs can function even in the absence of endogenous ligand binding. For example, it is well-recognized that a mutation in the rhodopsin GPCR, a known GPCR, leads to constitutive activation of that receptor, and that this constitutively activated rhodopsin receptor mutation leads to retinal degeneration manifested by retinitis pigmentosa. Generally, and as summarized in Arena’s patent application, “naturally” mutated versions of known GPCRs that result in constitutively active GPCRs are associated with well-defined disease states, based on what tissue expresses the mutant receptor.

20. In other words, it is my opinion that the scientific community recognizes that constitutively activated receptors have a biological function. In some cases, a constitutively activated receptor can be based upon an endogenous mutation that causes or results in a disease state. Indeed, the following table provides a list of diseases that are known to be associated with mutated, constitutively activated GPCRs:

Mutated, Constitutively Activated GPCR	Disease Condition
Thyrotropin receptor	Hyperthyroidism
Parathyroid hormone receptor	Parathyroidism
Lutenizing hormone receptor	Precocious puberty
Rhodopsin receptor	Retinitis pigmentosa
V2 vasopressin receptor	X-linked nephrogenic diabetes insipidus

To imply or state that constitutively activated receptors have no known function is, in my opinion, simply not a position that can be supported, scientifically or factually.

21. All of these concepts have only been recognized relatively recently. In my opinion, Arena's claimed invention is elegantly, advantageously and uniquely focused on these concepts in an area of interest to the academic and pharmaceutical communities, i.e., orphan receptors, and in particular, orphan GPCRs.

22. Because it was generally accepted that GPCRs had no function in the absence of binding by an endogenous ligand, it is sometimes, in my opinion, incorrectly assumed that one can not understand the function of a GPCR unless and until the endogenous ligand for that GPCR is first identified. In my opinion, this is a position that is not scientifically correct because the function of an orphan GPCR can be understood before the endogenous ligand is identified. Thus, with reference to the general concepts presented in my declaration, I address the positions taken by the PTO:

- a. *Because an orphan receptor does not have by definition a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease states.*

1(a). In my opinion, having reviewed Arena's patent specification, and being familiar with this scientific area, in my opinion, the basis for this position is incorrect. The premise of this position is that in order to understand the function of an orphan receptor, the proteins they modulate and the effects of orphan receptors on specific disease states, it is required that the endogenous ligand for that receptor must first be known. In my opinion, this premise is predicated upon the previously discussed, and incorrect, view that GPCRs are either "on" or "off" and that the endogenous ligand is required to turn the receptor "on." However, as outlined above, this is not a currently accepted view of GPCR function. In my scientific opinion, the location of a GPCR, by coupling this cellular localization within

specific cells, circuits, and organs, strongly links that GPCR to its physiological function, and with a more modern-based understanding of the equilibrium states of GPCR function, provides a primary tool in understanding receptor function. The skills and techniques for determining the location of a receptor within the body are routine and well established. In my opinion, all that is required is routine skill and an orphan receptor of interest to the scientist. Because the location of a receptor is useful in defining function, the ability to directly identify a compound defined by receptor functional activity, e.g., an inverse agonist, as opposed to receptor binding affinity, i.e., an antagonist, is important and very useful. By focusing on receptor function, as required by the claim language "inverse agonist" and "agonist" these classes of compounds, in my opinion, define far more than things that merely bind to a receptor, but rather a well-defined class of compounds that by definition must affect the function of the receptor, e.g., its signaling consequences and the genome's response to activation and/or inhibition of function. And, in my opinion, that desired functional outcome is based upon the location of the receptor and the inherent activity of the receptor in vivo, both of which are capable of being determined with skills and tools that are routine.

1(b). My opinion is not only based upon my twenty plus years of experiences in this area, but also views expressed by others and myself in the scientific literature. For example, as noted by Browne, M. J. in Biotechnology 78:247, 248 (2000): "Tissue-specific expression of genes can provide clues to their role in pathology." Wilson, S. et al in "Orphan G-protein Coupled Receptors: The Next Generation of Drug Target" British Journal of Biotechnology 125:1387, 1388 (1998) notes that "the expression pattern can determine whether a receptor is expressed in a normal or diseased tissue of interest as a therapeutic target", and that a "highly selective tissue expression profile can also provide a clue to receptor function." In my opinion, these views are well recognized in the art. Indeed, given the explosion of gene sequence information that is being provided to the art on an almost daily basis, it has become essential, and therefore quite common, to determine receptor expression patterns for an indication of receptor function.

2. In my opinion Arena has developed several elegant examples of allowing the location of an orphan GPCR to guide the process. I refer to the orphan receptors in this portion of my declaration by their Arena code name, but I have been informed and I believe that at the time of my declaration, these receptors are orphan GPCRs:

(a). **19AJ** I have reviewed data developed by Arena regarding a receptor referred to by Arena as 19AJ. Using routine techniques and commercially available reagents, procedures and kits, I have been informed and I believe that Arena determined that this receptor is expressed specifically in the beta cells in the islets of the pancreas. Because of the strong implications of the pancreas in insulin production, an appreciation for the role of this receptor was capable of being deduced based upon its location. Again using routine techniques and commercially available reagents, procedures and kits, I have been informed and I believe that Arena determined that this orphan GPCR has a very high basal activity level, i.e., it exists in a constitutively active state. This is an important point to be understood: in the case of 19AJ, identification of the endogenous ligand for 19AJ would be unnecessary based upon these data in that the receptor's function does not apparently require endogenous ligand binding for activation since it appears to exist in a spontaneously active state. Again

using routine techniques and commercially available reagents, procedures and kits, I have been informed and I believe that Arena determined that introduction of this receptor into insulin producing, glucose-responsive cell lines substantially increased insulin production. Thus, even in the absence of any knowledge of what the endogenous ligand for this receptor could be, its functional role can be appreciated, i.e., 19AJ is involved in insulin secretion. Because the claimed invention is focused on the direct identification of compounds based upon their functional activity, and not merely binding affinity, the selection process for an agonist in accordance with the teachings of the Arena patent, i.e., a compound that would further increase the functional activity of 19AJ, is scientifically based and logical. I have reviewed data that I have been informed and that I believe was developed by Arena whereby using high-throughput screening techniques, an agonist to the 19AJ receptor was directly identified, and that this compound, when used to treat glucose-tolerant cell lines, led to an increase in insulin production. Thus, not only can the location of the receptor be used to define the functional role of the receptor, but in the case of 19AJ, the endogenous ligand for this receptor was not needed to understand the function of 19AJ, and perhaps of greater importance, because 19AJ appears to be constitutively active, the ligand would be of little additional benefit for identification of compounds that can advantageously modulate the functional activity of this receptor. Indeed, since the receptor's endogenous ligand is typically utilized for finding receptor antagonists, in my opinion, based upon a review of the Arena data, a 19AJ antagonist would not be necessary.

(b). **18F** I have been informed and I believe that utilizing in situ hybridization, tissue samples were examined for expression of an orphan receptor referred to by Arena as 18F. I have been informed and I believe that Arena determined that the 18F receptor is expressed in the following areas of the brain: hypothalamus, hippocampus, nucleus accumbens, caudate and cerebral cortex. Given the high levels of expression of 18F in the areas of the brain associated with feeding, I have been informed and I believe that in situ hybridization analysis was conducted using routine protocols on both lean and obese male Zucker rats. Those in the art are aware that Zucker rats are genetically bred to result in animals that exhibit a lean or obese phenotype. In these studies, expression of 18F in the hypothalamus of the obese Zucker rats appears to be substantially increased as compared with the lean litter mate controls. In my opinion, the distribution of 18F in the hypothalamus indicated strong potential involvement in feeding behavior. Thus, in my opinion, the in situ hybridization analysis supports the functional position that 18F, an endogenous, constitutively active receptor, may play a role in obesity. In addition to in situ hybridization analysis, functional assessment can be accomplished by the protocol set forth in Marks, D.L. et al, 3 *Mol. & Cell. Neuro.* 395 (1992), which was utilized for assessment of co-localization of 18F and AGRP within the arcuate. The expression of AGRP is largely restricted to the arcuate nucleus (see Flier, J. S. and Maratos-Flier, E., and Figure 1 therein). The cells that produce AGRP also produce neuropeptide Y (NPY). Animal studies have evidenced that administration of AGRP and administration of NPY lead to increases in feeding behavior and obesity. AGRP has also been shown to have inverse agonist activity at the melanocortin 3 (MC3) and melanocortin 4 (MC-4) receptor; antagonism of the MC-4 receptor is also known to increase feeding behavior in obesity. Thus, AGRP appears to be involved in at least two pathways associated with feeding behavior. The data indicate that the 18F receptor is co-localized within cells that produce AGRP, and, coupled with the fact that 18F is an

endogenous, constitutively activated GPCR, it is apparent to me that 18F is in some manner a potential “regulator” of the system – based upon the data that I have reviewed, when expression of the 18F receptor is reduced via the use of antisense protocols there was an exceedingly rapid loss in body weight of the animals tested, suggesting that 18F may regulate the expression of AGRP. AGRP was analyzed in conjunction with radiolabeled 18F cRNA and both were found to be co-localized in the arcuate. Given the role that AGRP plays with respect to homeostasis, and further given that 18F is constitutively active in its endogenous state, the results obtained would be consistent with these data in that the almost immediate, significant loss of weight can be understood in the context of 18F influencing AGRP. Thus, in the case of 18F, the location of this receptor provides an indication of function, and using routine, and well known techniques, delving into the circuitry involved with this receptor provides a very good understanding of how modulation of the function of this receptor can be beneficially exploited for the possible treatment of disorders such as obesity. Most telling to me are the data that I have reviewed whereby Arena, using the claimed method, directly identified a small molecule chemical compound that is an inverse agonist to the 18F receptor, and when this small molecule is provided to test animals via oral administration, the data indicate that these animals decreased food consumption, increased fat metabolism, and lost weight. In my opinion, given the broad applicability of Arena's disclosed invention, the data developed using the 18F orphan receptor is strong evidence that absolutely weighs against the conclusion that the invention has no "real world use."

(c). *Tumorigenesis.* I have reviewed data that I have been informed and that I believe were developed by Arena regarding three orphan GPCRs expressed in tumor cells and cell lines. The data of **Appendix B** indicate that the 19Y receptor is over-expressed in uterine tumors (designated as “T”) and not in the corresponding normal tissues (designated as “N”), thus, in my opinion, implicating 19Y in uterine carcinogenesis (**Appendix B-1**). I have been informed and I believe that the 18A receptor was determined to be over-expressed in ovarian and breast cancer tissues, but not in the corresponding normal tissue, thereby implicating 18A in ovarian and breast cancer (**Appendix B-2**). I have been informed and I believe that the 18AI receptor is expressed in colorectal cancer cells (e.g., SW480), thus implicating 18AI in colorectal carcinogenesis (**Appendix B-3**). In these three examples, using routinely applied research techniques and skills well within the realm of scientists in this area, it is evident to me that these receptors, based upon their expression patterns, can be implicated in the pathological conditions, irrespective and without knowledge of their corresponding endogenous ligands. I further note that in these three examples, the orphan receptor mRNA is substantially up-regulated in apparent response to a defined condition, i.e., tumorigenesis. In my opinion, these examples indicate that a function for an orphan receptor can be ascertained without access to an endogenous ligand because of the readily ascertainable differential expression patterns in normal tissue versus abnormal or diseased tissue. In the case of 19Y, I have been informed and I believe that using the claimed methods, Arena has directly identified two small molecule chemical compounds that act as inverse agonists to the 19Y receptor; I have reviewed the data of **Appendix C**, and these data, coupled with the expression of 19Y in a cancerous condition, and not the non-cancerous condition, in my opinion indicate that the claimed method has provided an opportunity for development of a unique therapeutic

approach to uterine cancer. This is, in my opinion, an irrefutable real world use of the claimed invention.

(d). ***Regulation of Ischemic Damage.*** I have been informed and I believe that a sequence alignment conducted by Arena revealed that the 19BX receptor is homologous to complement 5a receptor ("C5a R"). C5a receptor is a chemattractant receptor that is involved in inflammation. A dot-blot analysis revealed that 19BX is expressed mainly in the brain (*see*, columns 1 and 2 of **Appendix D1 and D2**). Based upon these data, I have been informed and I believe that Arena conducted studies whereby in situ hybridization was utilized to discover that following MCA occlusion (momentary complete closure of the arteries found in the brain causing stoppage of blood and accumulation of blood pressure) and reperfusion (restoration of blood flow to the arteries), 19BX was abundantly expressed specifically in the ipsilateral cingulate cortex in a time dependent manner (**Appendix E, panels 1-9**). In situ hybridization also demonstrated that 19BX was expressed on the neurons of the hippocampus region. (**Appendix F**). Following the localization of 19BX expression in the neurons of the hippocampus, I have been informed and I believe that a Northern analysis was performed utilizing specific brain tissue from rat. This analysis confirmed the in situ hybridization that 19BX receptor is expressed on neurons located in the hippocampus. By utilizing routine techniques and commercially available kits, I have been informed and I believe that Arena determined that 19BX is a Gq linked receptor upon activation, i.e., the receptor signals through Gq protein -- as would be apparent, in my opinion, to one of ordinary skill in the art, these data are quite important for several reasons. Coupling of a receptor to the Gq protein is mediated by calcium [Ca²⁺]. Based upon the determination that the expression of 19BX increases in response to an ischemic condition; that 19BX is expressed on neurons; and that 19BX couples to Gq, this strongly implicates, in my opinion, that 19BX is involved in neuronal survival. Stated differently, when trauma occurs in the brain, 19BX is up-regulated, increasing the coupling to Gq, leading to an increase in calcium influx. An excessive amount of calcium in these cells will result in cell death. Thus, with a receptor of interest, 19BX, and routine skill, the data provide the opportunity to use the claimed invention to directly identify an inverse agonist to the 19BX receptor. Again, in my opinion, a real world use for the claimed invention.

(e). ***Regeneration of Nerve Cells.*** I have been informed and I believe that Arena conducted certain studies whereby a Northern analysis revealed that 19M is expressed in Schwann cells (**Appendix G1**). As those in the art appreciate, Schwann cells act to regenerate injured nerves (or axons) by forming myelin sheaths around the axons, thus providing an insulation of myelin sheaths. The importance of myelination is to conserve metabolic energy, i.e., action potential travel at a faster rate when there is such insulation. I have also been informed and I also believe that 19M is over-expressed in crushed rat sciatic nerves (**Appendix G2**). Based upon these data, it is my opinion that the functional role of this orphan GPCR can be deduced, e.g., 19M plays some role in regenerating nerve cells. In this example, then, it is my opinion that the power of the claimed invention can be recognized: in some diseases, hyper-myelination is a concern, while in other diseases, hypo-myelination is a problem; the claimed invention provides the opportunity to secure inverse agonists and agonists to the 19M receptor such that, in the case of hyper-myelination (e.g.,

tumorigenesis), a 19M inverse agonist would be preferred, while a 19M agonist would be preferred where hypo-myelination occurs (e.g., a degenerative disease such as diabetes).

3. I have been informed and I believe that the foregoing are representative. I further note that as a company, Arena is not yet four years old, and has only had a fully operational lab for about three years. In my opinion, the body of work developed in this area by this small company of about 75 scientists is remarkable. By following the teachings of the claimed invention, it is my opinion that as with the Arena scientists, those having routine skill and an orphan receptor of interest can use the claimed invention as disclosed. In my opinion, based upon my over twenty plus years as a scientist, it is simply not plausible to assert that the claimed invention has no real world use or that a well established utility for the claimed invention is lacking: the teachings of the patent application; the use of defined terms such as “inverse agonist” and “agonist” in the claims; the data developed by Arena; the licensing of the technology by Arena to well-known and established pharmaceutical companies such as Eli Lilly; the publication by Glaxo Wellcome regarding the use of orphan receptors; the skill level of scientists in this field; the relatively limited number of orphan GPCRs that are and will be available via the efforts of the mapping of the human genome; the ability to use commercially-available reagents and kits and techniques to define the primary G protein that initiates the orphan GPCR’s transducing pathway; the ease by which a skilled scientist can understand the differential expression of an orphan receptor of interest in a normal versus a disease state; and, the ability to understand the functional role of an orphan receptor before its endogenous ligand is identified, all collectively, in my opinion, totally vitiate the position taken by the PTO that “[b]ecause an orphan receptor does not have by definition a corresponding endogenous ligand that is known, the specification nor the art of record disclose the function of orphan receptors, the proteins they modulate and their effects on specific disease states.” It is my scientific opinion that this position can not be sustained.

b. Similarly, constitutively activated orphan receptors have no known function.


1. As the 19AJ and 18F examples illustrate, this position is simply untenable, scientifically and factually. Nature has apparently established, in the case of 19AJ and 18F, GPCRs that are constitutively active in the test systems used by Arena and that are highly active in their endogenous states. While the reason for this may not be completely understood, it is certainly reasonable to speculate that as signal-transducers, 19AJ and 18F are functionally active for important biological reason. But irrespective of this speculation, 19AJ and 18F are examples of constitutively active orphan receptors, some functions of which Arena has been able to ascertain via localization, pharmacology and regulatory events. Further, as indicated above in the table of paragraph 20, there are diseases that are associated with “natural mutational mechanisms” producing highly or constitutively active receptors, thereby leading to natural pathologies. As I have previously indicated, the range of signaling activation in GPCRs, whether orphan or known, is quite wide covering the range from almost completely silent (without its endogenous agonist) through highly activated systems which are only minimally driven to higher levels of activation by their endogenous ligands. The fact that orphan receptors exist in biological systems means that these receptors have a function; these may be constitutively activated orphan receptors such as 19AJ and 18F. To assert that

constitutively activated orphan receptors have no known function, in my opinion, is both scientifically and factually incorrect.

23. In all of the examples discussed in my declaration, it is my opinion that directly identifying inverse agonists or agonists in accordance with the claims and the specification and the skills of a scientist in this field, provide a unique opportunity to secure compounds for modulating these receptors, their associated biological systems and related pathologies. In short, I do not agree with the position that there is no "real world use" for the claimed invention. This conclusion, in my opinion, is inconsistent with substantial evidence to the contrary, and, therefore, incapable of being supported. In short, using the PTO's phrase, I am of the opinion that there is a well established utility for the claimed invention.

I further declare that statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 2 day of November, 2000 at Ann Arbor, Michigan.



Stanley J. Watson, M.D., Ph.D.
